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10/733,776	12/12/2003	Mechthild Rieping	7601/80921	9536

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,776	RIEPING, MECHTHILD	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,41-49,52,55,56 and 58-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38, 41-49, 52, 55-56, and 58-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 38, 41-49, 52, 55-56, and 58-64 are pending in the application.

[2] Applicant's amendment to the claims, filed on 10/28/08, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Receipt of an English-language translation of German Application 103 03 571.0 is acknowledged.

[4] Applicant's arguments filed on 10/28/08 in response to the Office action mailed on 6/16/08 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, Second Paragraph

[6] Claims 38, 41-47, 55-56, and 58-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 38 (claims 41-47 dependent therefrom) and 55 (claims 56 and 58-61 dependent therefrom) are confusing as requiring the bacterium to have the *yjgF* open reading frame of SEQ ID NO:1 that encodes SEQ ID NO:2, yet simultaneously has a *yjgF* open reading frame that has undergone modification that would appear to alter the

structure of SEQ ID NO:1. It is unclear as to how the bacterium has the *yjgF* open reading frame of SEQ ID NO:1 and simultaneously has a *yjgF* open reading frame that has undergone modification. It is suggested that applicant clarify the meaning of the claims, *e.g.,* by indicating that the *yjgF* open reading frame *prior to modification* has the nucleotide sequence of SEQ ID NO:1 and encodes SEQ ID NO:2.

Claim Rejections - 35 USC § 112, First Paragraph

[7] Claims 38, 41-49, 55-56, and 58-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a process for producing an L-amino acid as recited in the claims using a genus of *Escherichia* bacteria with a modified *yjgF* gene, wherein the modification(s) are set forth in the claims.

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

CLAIM INTERPRETATION: Claims 38 and 55 require the modification to result in increased production of L-threonine. The modifications of claims 38 and 55 do not necessarily result in deletion of the open reading frame or encoding a *yjgF* protein with reduced or eliminated activity. For example, the phrase "deletion of...part of the *yjgF* open reading frame" can be deletion of one or more contiguous or non-contiguous nucleotides at any location along the open reading frame and "insertional mutagenesis due to homologous recombination" can insert or more amino acids into the sequence at any location(s) along the open reading frame. Also, it is noted that the modified *Escherichia* bacterium of the claims is a product-by-process, essentially encompassing any *Escherichia* bacterium with a single modification as encompassed by the claims, *e.g.,* deletion of a single codon, in addition to any other modification(s) to any other nucleic acid, as long as the bacterium has increased L-threonine production.

Also, the bacterium of claims 38, 48, and 55 requires that the "the *yjgF* open reading frame...has the nucleotide sequence of SEQ ID NO:1" (claims 38 and 55) and/or "encodes the polypeptide of SEQ ID NO:2" (claims 38, 48, and 55), sequences of *E. coli yjgF* open reading frame and encoded polypeptide, yet is not limited to *E. coli,* but to any bacterium within the genus of *Escherichia.*

MPEP 2163.II.A.2.(a).i) states, "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical

properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention".

The specification discloses the reduction to practice of a single representative species of the genus of modified *Escherichia* bacteria that have a *yjgF* open reading frame encoding SEQ ID NO:2 (claims 38, 48, and 55) having the nucleotide sequence of SEQ ID NO:1 (claims 38 and 55) and having increased L-threonine production, *i.e.,* *Escherichia coli* with deletion of the *yjgF* open reading frame of SEQ ID NO:1, wherein deletion results in an inactivated *yjgF* open reading frame. There are no other drawings or structural formulas disclosed of a modified *Escherichia* bacterium as encompassed by the claims. There is no prior-art or disclosed teaching regarding which species among the genus of *Escherichia* bacteria – if any – have a *yjgF* open reading frame encoding SEQ ID NO:2 and comprising SEQ ID NO:1 and, other than *E. coli,* there is no disclosed or art-recognized correlation between a *yjgF* open reading frame comprising SEQ ID NO:1 and an *Escherichia* bacterium. Also, there is no prior-art or disclosed teaching regarding which modification(s) to SEQ ID NO:1 as encompassed by the claims that will result in increased production of L-threonine and there is no disclosed or art-recognized correlation between any structure other than deletion of SEQ ID NO:1 or an inactivating modification of the open reading frame of SEQ ID NO:1 such that the deletion or modification results in an encoded protein with reduced or eliminated activity relative to SEQ ID NO:2.

Accordingly, one of skill in the art would not accept the disclosure of *Escherichia coli* with deletion of the *yjgF* open reading frame of SEQ ID NO:1 or an inactivating modification of the open reading frame of SEQ ID NO:1, wherein the deletion or the modification results in an inactivated *yjgF* open reading frame as being representative of other *Escherichia* having a modified *yjgf* open reading frame that optionally results in increased L-threonine production as encompassed by the claims. As such, the specification, taken with the pre-existing knowledge in the art, fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

[8] Claims 38, 41-47, 55-56, and 58-61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for increased production of L-threonine using an *Escherichia coli* with deletion or modification of the *yjgF* open reading frame of SEQ ID NO:1, wherein deletion or modification results in an inactivated *yjgF* open reading, does not reasonably provide enablement for a process for increased production of L-threonine using all *Escherichia* bacterium having any modification as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation is required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows:

(A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. The Factors considered to be most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The claims encompass an *Escherichia* bacterium having any modification as encompassed by the claims that results in an increased production of L-threonine. As noted above, the modifications are not limited to those that result in an inactivated *yjgF* open reading frame. For example, the phrase "deletion of...part of the *yjgF* open reading frame" can be deletion of one or more contiguous or non-contiguous nucleotides at any location along the open reading frame and "insertional mutagenesis due to homologous recombination" can insert or more amino acids into the sequence at any location(s) along the open reading frame. Also, it is noted that the modified *Escherichia* bacterium of the claims is a product-by-process, essentially encompassing any *Escherichia* bacterium with a single modification as encompassed by the claims, *e.g.*, deletion of a single codon, in addition to any other modification(s) to any other nucleic acid, as long as the bacterium has increased L-threonine production.

The enablement provided by the specification is not commensurate in scope with the claims, particularly with regard to the scope of modified *Escherichia* bacterium with increased L-threonine production.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The prior art does not appear to expressly teach any modification(s) of the *E. coli yjgF* open reading frame to achieve enhanced L-threonine production. Moreover, the effect(s) of modifying an encoding open reading frame on the corresponding encoded polypeptide's activity are highly unpredictable. See, *e.g.,* pp. 13-15 of the Office action mailed on 7/13/05 and p. 12 of the Office action mailed on

The amount of direction provided by the inventor and The existence of working examples: In this case, the specification discloses only a single working example of an *Escherichia* bacterium with increased production of an L-amino acid, *i.e., Escherichia coli* with deletion of the *yjgF* open reading frame of SEQ ID NO:1, wherein deletion results in an encoded protein with reduced or eliminated activity relative to SEQ ID NO:2. See specification at pp. 23-26, Examples 1-4. Other than this single working example, the specification fails to disclose any other modifications that result in an *Escherichia* bacterium with increased production of L-threonine.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of mutagenesis and homologous recombination were known at the time of the invention, it was not routine to alter an *Escherichia* open reading frame of SEQ ID NO:1 by any modification(s) as encompassed by the claims to achieve an *Escherichia* bacterium having increased production of L-threonine.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by

the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

[9] The rejection of claims 38-47 under 35 U.S.C. 102(e) as being anticipated by Kruse et al. (US Patent Application Publication 2007/0092950; "Kruse1") is withdrawn in view of applicant's submission of an English-language translation of the foreign priority document, German application 103 03 571.0. See MPEP 706.02(b).

[10] The rejection of claims 38-47 under 35 U.S.C. 102(e) as being anticipated by Kruse et al. (WO 2005/014841; "Kruse2") is withdrawn in view of applicant's submission of an English-language translation of the foreign priority document, German application 103 03 571.0. See MPEP 706.02(b).

Claim Rejections - 35 USC § 103

[11] The rejection of claims 38, 41-49, and 52 under 35 U.S.C. 103(a) as being unpatentable over Volz (*Protein Sci* 8:2428-2437, 1999; cited in the IDS filed on 11/18/2004) in view of Enos-Berlage et al. (*J. Bacteriol* 180:6519-6528, 1998; cited in the IDS filed on 11/18/2004; "Enos-Berlage"), Verkhovskaya et al. (*Microbiol.* 147:3005-3013, 2001; "Verkhovskaya"), and Promega Technical Bulletin No. 117 (September, 2002) is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 11 beginning at p. 11 of the Office action mailed on 6/16/08. Newly added claims 62-64 are included in the instant rejection for reasons of record addressing claims 45-47. Thus, claims 38, 41-49, 52, and 62-64 are rejected herein.

RESPONSE TO ARGUMENT: Beginning at p. 7 of the instant remarks, applicant maintains the position that there is no teaching or suggestion in the cited references to use a bacteria with a deleted *yjgF* gene for L-threonine production.

Applicant's argument is not found persuasive. The examiner does not dispute applicant's position that the objective of the combination of references is *not* amino acid isolation. However, the examiner maintains the position that, by practicing the method suggested by the combination of references, one would have practiced each of the active method steps of the claims.

Beginning at p. 9 of the instant remarks, applicant argues the method suggested by the combination of references "may enrich a preparation of amino acids", this is a transient isolation as the steps involved in the method ultimately eliminate rather than

isolate or recover amino acids. Applicant argues this is an unreasonable interpretation of the claims.

Applicant's argument is not found persuasive. Initially, it is noted that nowhere in the method suggested by the combination of references, which ultimately results in preparation of a cell-free lysate, which applicant admits is an enrichment of a preparation of amino acids, ultimately results in elimination of the amino acids. Here, the cell-free lysate would contain L-threonine as a product of L-amino acid biosynthesis by the *E. coli*. It is noted that L-amino acid biosynthesis, including L-threonine, by *E. coli* is well-known and established in the prior art and thus one of ordinary skill in the art at the time of the invention would have recognized that by practicing the method of Enos-Berlage using an *E. coli* with an inactivated *yjgF* gene would have isolated L-threonine. Although applicant argues that Enos-Berlage teaches that *yjgF* mutation are suggested to block, not promote amino acid production, it is noted that the reference only suggests that "yjgF mutaton results in partial block of at least one step in *isoleucine* biosynthesis" (emphasis added). Moreover, the mutation is described as resulting in a "partial block", not a *complete* block of the step in isoleucine biosynthesis. Also, there is no mention of the mutation affecting L-threonine biosynthesis and because the mutation affects a step *subsequent* to the reaction catalyzed by threonine deaminase. The biosynthetic pathways of L-threonine and L-isoleucine are well-known in the art and it is known that threonine deaminase catalyzes the conversion of threonine to alpha-ketobutyrate, followed by reactions that do not involve L-threonine. See, *e.g.*, pp. 770-773 of Voet et al., "Biochemistry, 2nd Edition", John Wiley and Sons, Inc., New York, 1995. As such,

one of ordinary skill in the art would have no expectation that the mutation would negatively affect L-threonine biosynthesis.

While applicant asserts L-threonine is an "end product" and appears to take issue with the examiner's interpretation of the isolating and/or recovering steps, as noted in prior Office actions, these steps have been interpreted in light of the specification's disclosure that "the desired L-amino acid is isolated, constituents of the fermentation broth and/or the biomass in its entirety or portions (> 0 to 100%) thereof optionally remaining in the product" (see original claim 2 and specification at p. 4, lines 6-9). In view of this disclosure, the term "isolation" is clearly intended by applicant to be interpreted as meaning constituents of the fermentation broth and/or the biomass in its entirety or portions (> 0 to 100%) thereof optionally remain *in the product*. Based on the specification's characterization of "isolation", one of ordinary skill in the art would clearly recognize a cell free lysate or even a whole cell culture as being encompassed by the claims. While the definition of "isolation" as provided in the specification and original claims may be different from the ordinary and customary meaning of the term, as noted in MPEP 2111.01.IV, "An applicant is entitled to be his or her own lexicographer". See also MPEP 2173.05(a), which states, "When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art". If applicant maintains this interpretation is unreasonable, applicant is requested to clarify why the examiner's interpretation is unreasonable in light of the specification's characterization of the term "isolation".

Beginning at p. 9, Applicant argues the rejection is based on a process that is not the same as the claimed method and then alleged the claimed process would be inherent to the process suggested by the combination of references, which applicant characterizes as a novelty rejection. According to applicant, there is no such thing as inherent obviousness.

Applicant's argument is not found persuasive. It appears that applicant takes the position that the method suggested by the prior art as set forth in the rejection at pp. 6/16/08 of the Office action does not teach all limitations of the claims. However, as noted above, the combination of references teaches a method that practices each and every one of the recited active steps. As such, contrary to applicant's position, the steps of the method as suggested by the prior art are the *same* as the recited method steps. Claim 38 requires increased L-threonine production (claim 48 does not) and while there is no dispute that the combination of references does not expressly teach increased L-threonine production, this would have been an inherent result of inactivating the *E. coli yjgF* gene and culturing the resulting *E. coli* as suggested by the prior art, which appears to be undisputed by applicant. See MPEP 2112.02, which states, "When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process".

[12] In the event applicant provides a line of reasoning and/or evidence that batch, fed batch, and repeated fed batch culturing methods are not art-recognized equivalents,

the rejection of claims 46-47 under 35 U.S.C. 103(a) as being unpatentable over Volz in view of Enos-Berlage, Verkhovskaya, and Promega Technical Bulletin as applied to claims 38, 41-45, 48-49, 52, and 62 above and further in view of Lee (*Trends Biotechnol.* 14:98-105, 1996) is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 12 beginning at p. 14 of the Office action mailed on 6/16/08. Newly added claims 63-64 are included in the instant rejection for reasons of record addressing claims 46-47. Thus, claims 46-47 and 63-64 are rejected herein.

RESPONSE TO ARGUMENT: Applicant does not dispute the examiner's position that batch, fed batch, and repeated fed batch culturing methods are art-recognized equivalents. However, in the event such an argument is raised as a basis for traversal, the rejection is maintained.

[13] The rejection of claims 48-57 under 35 U.S.C. 103(a) as being unpatentable over Kruse1 OR Kruse2 is withdrawn in view of applicant's submission of an English-language translation of the foreign priority document, German application 103 03 571.0. See MPEP 706.02(b).

Conclusion

[14] Status of the claims:

Claims 38, 41-49, 52, 55-56, and 58-64 are pending.

Claims 38, 41-49, 52, 55-56, and 58-64 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656